Cardiac ryanodine receptor mutations linked to arrhythmia and sudden death alter the threshold for store-overload-induced Ca^{2+} release

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CPVT (catecholaminergic polymorphic ventricular tachycardia) is an inherited life-threatening arrhythmogenic disorder. CPVT is caused by DADs (delayed after-depolarizations) that are induced by spontaneous Ca^{2+} release during SR (sarcoplasmic reticulum) Ca^{2+} overload, a process also known as SOICR (store-overload-induced Ca^{2+} release). These Ca^{2+} release events occur through the cardiac ryanodine receptor (RyR2) with most instances of CPVT being attributed to mutations within RyR2. Using cytosolic and intra-SR Ca^{2+} imaging we have found that many of these CPVT-associated RyR2 mutations lead to SOICR by increasing the sensitivity of RyR2 to SR Ca^{2+}, effectively reducing the SR Ca^{2+} load at which SOICR occurs (Jones *et al.*, 2008) (see Figure). This is in keeping with the phenotype of CPVT where arrhythmias only occur during periods of stress, a condition known to increase SR Ca^{2+}.

Subsequently, we and our collaborators have extended these studies and have found that sensitization of RyR2 to SR luminal Ca^{2+} activation represents a common mechanism of DADs and arrhythmia. To date we have shown that pro-arrhythmic drugs (Kong *et al.*, 2008), phosphorylation of RyR2 (Xiao *et al.*, 2007), and alterations in the macro-molecular complex surrounding RyR2 (Zhang *et al.*, 2013) all result in sensitization of RyR2 to luminal Ca^{2+}. However, not all SOICR events are created equal, as using a CPVT mutant mouse, that also has an altered SR Ca^{2+} store, we have recently demonstrated that frequent but small SOICR events do not lead to DADs and arrhythmia whereas scarcer but larger SOICR events almost always trigger DADs and arrhythmia (Bai *et al.*, 2013). This suggests that both the occurrence and magnitude of SOICR events are important factors in determining whether arrhythmia will occur. Perhaps most excitingly, we have not only shown that the occurrence of SOICR is arrhythmogenic but that its inhibition is very effective at preventing CPVT mediated arrhythmia (Zhou *et al.*, 2011). Given we have shown that aberrant regulation of RyR2 by multiple factors can trigger SOICR and arrhythmia, combining these data suggests that anti-SOICR agents targeting the threshold for store-overload-induced Ca^{2+} release may represent a new class of drugs for preventing many types of arrhythmogenic disorders.

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